Review Article

Catecholamines, Steroids and Immune Alterations in Ischemic Stroke and Other Acute Diseases

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ABSTRACT: The outcome of stroke patients is not only determined by the extent and localization of the ischemic lesion, but also by stroke-associated infections. Stroke-induced immune alterations, which are related to stroke-associated infections, have been described over the last decade. Here we review the evidence that catecholamines and steroids induced by stroke result in stroke-induced immune alterations. In addition, we compare the immune alterations observed in other acute diseases such as myocardial infarction, brain trauma, and surgical trauma with the changes seen in stroke-induced immune alterations.

Cerebrovascular diseases, including ischemic stroke, are the second most common cause of death worldwide after ischemic heart disease; stroke is the third leading cause of death in the USA [1, 2]. Stroke-related disability ranks third when disability-adjusted life-years are assessed [3]. The clinical outcome of stroke patients is not solely determined by the infarct size and localization, but is also altered by subsequent infections. Stroke-associated infections (SAIs), of which pneumonia is the most common, impair outcome and increase mortality [4, 5]. The frequency of SAIs ranges from 15%-42% depending on the inclusion criteria of the respective study [4, 5]. In recent years it has become evident that increased susceptibility to infections is related to stroke-induced alterations in the immune system. Loss of lymphocytes, lymphocyte dysfunction, and monocyte deactivation following stroke have been observed in both experimental stroke models and in stroke patients [6-8].

If the mechanisms by which stroke induces these immune alterations became known, these pathways could be targeted in future therapeutic trials. The central nervous system and the immune system communicate with each other via several pathways: the sympathetic nervous system, the parasympathic nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis [9]. These pathways can be triggered through the nervous system by the brain itself or as a response to afferent vagus stimulation. In addition, the immune system can induce a stress response through inflammatory cytokines, which may be locally produced or may reach the central nervous system via the blood stream. Ischemic brain injury has been shown to affect several of these pathways [9].

Catecholamine effects and receptors on immune cells

To alter immune responses, catecholamines must be present in the microenvironment of the leukocytes, and the cells must express a receptor to detect these hormones [10]. Direct sympathetic innervation is found in both primary and secondary lymphoid organs, where norepinephrine and epinephrine are released from the sympathetic nerve endings and immune cells express α- and β-adrenoreceptors that transduce the signal into the cell (Table 1) [10]. Expression levels differ due to epigenetic regulation by histones and DNA methylation [11-13].

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Table 1. Expression of adrenoreceptors on immune cells.

Most innate immune cells	Both αAR and βAR families
Bone marrow-derived dendritic cells	α1AR α2AR β1AR β2AR
Monocytes/macrophages	β2AR α1AR α2AR
Natural killer cells Resting and activated B cells Naïve T cells and Th1 cells, but not Th2 cells	β2AR
Regulatory T cells and Th17 cells	No data available

Reviewed in [14]. AR, adrenoreceptor.

Since lymphocytes are primed in lymphoid organs, and catecholamine concentrations within the spleen and lymph nodes are likely to exceed plasma concentrations due to direct sympathetic innervations, sympathetic activation can effectively alter immune responses [15]. Furthermore, catecholamines are not only released from nerve terminals and the adrenal medulla, but can also be actively produced, stored, and secreted by immune cells themselves [16]. Catecholamines released from immune cells serve as auto/paracrine regulators of lymphocyte activity, for example through the suppression of lymphocyte proliferation, cytokine production, and the induction of apoptosis [17, 18]. The biological relevance of immune cell-derived catecholamines versus the catecholamines released by the sympathetic response is not known [19].

Catecholamine release leads to a quick two-phased mobilization: initial lymphocytosis is succeeded by granulocytosis and reduced lymphocytes in the peripheral blood. Lymphocyte recruitment seems to mainly be mediated by β2-adrenoreceptors (β2AR) and originates from the marginal pool and the spleen, whereas granulocytes are predominantly recruited from the marginal pool and the lung via α-adrenoreceptor stimulation [20]. While this biphasic response of lymphocytes to β2AR engagement is well described the underlying mechanisms are only partly resolved. The effect depends on the time of receptor engagement in relation to the activation and differentiation state of the cell, the involved molecular signaling pathway, and the cytokine microenvironment (Table 2) (for reviews see [21-23]). In addition, high concentrations of catecholamines are known to induce lymphocyte apoptosis [17].

Glucocorticoid effects and receptors on immune cells

Another effective pathway for the interaction of the central nervous system and the immune system is the HPA axis. Activation of the HPA axis starts with the release of corticotropin-releasing hormone from the hypothalamus, which induces the secretion of adrenocorticotropic hormone, which leads to the secretion of glucocorticoids from the adrenal gland [10]. Glucocorticoids have long been known to exert anti-inflammatory and immunosuppressive effects, and are broadly used as an anti-inflammatory treatment. In the absence of ligands, the glucocorticoid receptor (GCR) resides in the cytoplasm in a complex with heat shock proteins and immunophilins [24]. The GCR is constitutively expressed in virtually all cell types, but different tissue-specific expression patterns lead to tissue-specific outcomes in different diseases [25].

When binding its ligand in the cytoplasm, the GCR can interact with signaling pathways of the T-cell receptor signaling complex and thus modulate pro-inflammatory gene expression [26]. The primary actions of the GCR are evident in the nucleus. Upon ligand binding, chaperone complex remodeling exposes nuclear localization sequences on the GCR, leading to its nuclear translocation [27]. The GCR has two ways of modulating gene expression. As a dimer, GCR binds the glucocorticoid response element, when undimerized, GCR binds pro-inflammatory transcription factors such as AP-1, NF-kB, IRF-3, STAT, CREB, NFAT, T-bet, and GATA-3, leading to their inhibition [27]. Further details are reviewed in [28]. Cellular effects of stress hormones are summarized in Table 2.

Table 2. Cellular effects of stress hormones in immune cells

	Glucorticoids	**Catecholamines**
DC	- induce apoptosis in immature DCs [29] - reduction of MHCII, costimulatory molecules and cytokine expression [30, 31] - inhibition of migration in vivo and in vitro [32]; [33] by downregulation of CCR7 [34] - induction of a tolerogenic DC phenotype that induces T cell anergy, suppression of T cells and generates Tregs [35]	- enhanced surface expression of MHCII, CD80 and CD86 [36] - control cell migration via α1bAR [37] and induction of an anti-inflammatory cytokine profile [38] - enhancement of IL-33 production thus promoting Th2 responses [39] inhibited the lipopolysaccharide (LPS)-stimulated production of interleukin (IL)-23, IL-12 p40, tumor necrosis factor (TNF)-alpha and IL-6 [40]
Macrophages/ monocytes	- suppressed activation by IL-10 induction and inhibition of upregulation of pro-inflammatory CD163 [41] - development of myeloid suppressor cell like phenotype [42]	- cAMP/PKA dependent stimulation of IL-10 promoter/enhancer [43] - upregulate L-selectin in vitro [44] - inhibit IL-6 secretion via αAR [45] but - induce secretion of IL-6 (in the presence of GC) via βAR [46]
Neutrophils	- suppression of adhesion molecule expression inhibits rolling, adhesion and transmigration [47] - increase of BM-derived neutrophils in blood [48] - promotes necrosis [49]	- increase the total circulating neutrophil pool for a few hours [50] - increase expression and release of Hsp72 [51] - suppression of CD11b and inhibition of suppression of CD62L (L-selectin) [52] - decreased phagocytosis of zymosan in vitro [53]

B cells	- reduction of splenic and LN B cell numbers
	 - inhibit B cell progenitor proliferation
	 - enhance IgE, suppressed IgG production [54, 55]
		- state of B cell activation decisive about effect of CA:
		  - enhanced IgG1 production and IgE on NE exposure during antigen processing or after Th2 coculture [56]
		  - increase in costimulatory capacity (CD86 upregulation) [57]
		  - β2AR engagement in presence of IL-4 enhances IgE [58]

T cells	- affect thymocyte maturation by inducing apoptosis in thymocytes; more sensitive than Teff than Treg cells [59, 60]
	 - physiological doses: shift from Th1 response to Th2 [61]
	 - pharmacological doses induce anti-inflammation:
	  - reduce RORγt in Th17 cells [62]
	  - inhibit TH1 function by direct inhibition of STAT4 and T-bet [63, 64]
	  - suppress STAT6 function in Th2 by interfering with GATA [65, 66]
		- β2AR engagement enhances IFNγ production in TH1 cells the presence of IL-12 in pre activated TH1 cells [67]
		 - inhibit IFN-γ in resting TH1 cells [13]

NK cells	- impair NK cell function via histone deacetylation and transrepression [68]	- inhibit NK cytotoxic functions by:
		  - reduced TNF-α, IFN-γ, and GM-CSF
		  - impaired, target binding [69]

DC dendritic cells; CCR C-C chemokine receptor; NK natural killer cells;
Treg regulatory T cells; Teff effector T cells; BM bone marrow; LN Lymph node; NE norepinephrine; CA Catecholamine.
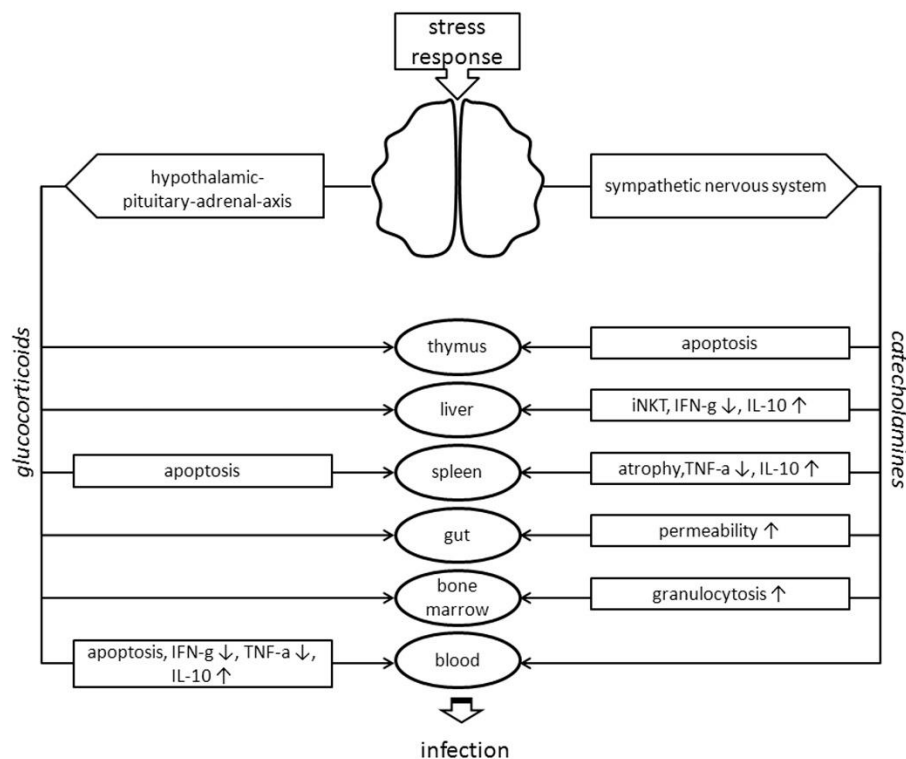
Figure 1. Systemic effects of the stress response in ischemic stroke. The scheme depicts those organ specific immune alterations that occur in stroke and have been experimentally linked to the activation of either the HPA axis or the sympathetic nervous system. As a result the stress response reduces the ability to fight bacteria and increases the risk of subsequent infection. (HPA, hypothalamic-pituitary gland-adrenal; iNKT, invariant natural killer T cells; IFN-g, Interferon-gamma; IL-10, Interleukin-10; TNF-a, tumor necrosis factor-alpha; ↑, increase, ↓, decrease)

Stress responses have been described in stroke; the pathways delineated above have been implicated in stroke-induce immune alterations (SIIAs). In this article, we review the clinical and experimental evidence that stress hormones are indeed the mediators linking ischemic brain injury with SIIA. Other acute diseases such as myocardial infarction (MI), surgical trauma, and trauma-related injury also induce a stress response. We will summarize what is known with respect to immunological changes in patients with these diseases (section 4.1), and discuss whether changes observed in SIIA that enhance the risk for SAIs are unique to ischemic brain injury or extend to other diseases. This review will not address the role of the immune system and SIIAs in secondary immune-mediated organ damage, which has been described in experimental stroke and traumatic brain injury (TBI) [70-73].

Stress hormones in stroke

Alterations induced by catecholamines and steroids in specific organs are summarized in Figure 1. Here we will

focus on cell type specific alterations and clinical consequences.

Stroke: catecholamines and clinical outcome

Several studies of stroke patients have investigated whether epinephrine, norepinephrine, or its metabolites metanephrine and normetanephrine can be used as markers for the extent of SIIA and whether these molecules correlate with patient outcome and the occurrence of SAIs. Metanephrine and normetanephrine, which lack biological activity but are relatively stable, can be determined in urinary samples [74]. Data across different stroke patient populations and research groups consistently indicate that catecholamines are associated with an increased risk of post-stroke infections. Higher levels of metanephrine and normetanephrine on admission and on day 1 enhance the risk of developing SAIs [4, 75, 76]. In agreement with these findings, mortality at 3 months was associated with higher levels of

normetanephrine on admission and day 1, at least in one study [75].

Furthermore, the cellular changes observed in SIIA, including lymphocytopenia and reduced monocytic HLA-DR expression that leads to impaired immune function, have been linked to catecholamine levels in stroke patients in the ESPIAS and PANTHERIS studies [4, 75]. This observation may be due to the biphasic effect of catecholamines on immune cells, including the autocrine, apoptosis-inducing regulation that was described earlier. However, the observation that lymphocytes remaining in the circulation of stroke patients are primed towards proinflammation [76] is not in line with the earlier report that Th2 cells lack the β2AR [13], and therefore T cells with an anti-inflammatory phenotype should escape catecholamine-induced apoptosis. This scenario suggests that additional mediators are involved in regulating T-cell responses in stroke patients.

The phenotypic findings in human stroke-induced SIIA are very similar to the observations made in experimental stroke; lymphocyte apoptosis in the spleen and thymus, lymphocytopenia in the periphery, and a defective interferon (IFN)-γ response in monocytes predispose patients to post-stroke infections, with bacteremia and spontaneous pneumonia in experimental stroke [77]. Thus, the animal model appears well suited to investigate the underlying pathophysiology of SIIA.

Selective inhibition of the effects of sympathetic nervous-system activation at an early time point, but not the blockage of the effects of HPA axis activation, prevented systemic infections and improved survival in stroked mice [77, 79]. These findings suggest that catecholamines, but not glucocorticoids, are causally related to SAI. Moreover, adoptive transfer of splenocytes, especially T and natural killer cells from control mice into stroked animals, restored the recipient's defense against pathogens [77]. Both the loss of lymphocytes due to apoptosis and the functional impairment of lymphocytes can be explained by the known β2AR-mediated effects of catecholamines. Additionally, adrenoreceptor antagonism has been demonstrated to inhibit splenic atrophy, reduce the infarct volume, and modulate cytokine expression in the spleen following experimental stroke, but did not affect a specific lymphocyte population within the splenocyte fraction [80]. Thus converging evidence from animal models and human studies support the role of β-adrenergic stimulation in SIIA.

Stroke: glucocorticoids and clinical outcome

The stress hormone cortisol is also transiently elevated following stroke [81-83]. However, the data for the kinetics of cortisol in plasma concentrations as well as the relationship of cortisol with SAI remain contradictory. The increase of plasma cortisol levels has been reported to persist through day 5 post-stroke [81] , while others observed elevated plasma levels on admission that normalized within 24 h [84, 85].

The correlation of cortisol levels with stroke severity, infarct volumes, unfavorable outcome, and even higher mortality has been repeatedly demonstrated [86-90]. However, the association of cortisol levels with markers of SIIA and post-stroke infections remains poorly understood. Whereas our own data support an association of plasma cortisol levels on day 1 with SAI [76] , other studies detected no association of plasma cortisol levels with SAI or with monocyte function [4, 84]. Another study linked interleukin (IL)-6 levels to cortisol levels; in stroke patients, IL-6 levels correlated significantly with cortisol levels, and morning serum IL-6 levels independently predicted evening/night cortisol levels, which has been interpreted as evidence for cytokine-induced HPA axis activation following stroke [91].

In experimental stroke, a three-fold increase in serum corticosterone levels (the primary glucocorticoid in rodents) compared to naïve animals was observed at 4 h after stroke; only 24 h after sham/permanent middle cerebral artery occlusion surgery, corticosterone levels in stroked animals returned nearly to the levels of naïve animals [92].

While several studies have addressed the role of glucocorticoids in brain-lesion development in stroke, there is a surprising paucity of data investigating the effects of glucocorticoids on immune function and infection in experimental stroke. The seminal study by Prass et al. has long been the only investigation of GCR antagonism with respect to SIIA and SAI. They reported that glucocorticoid inhibition reduced apoptosis of splenocytes and lymphopenia following stroke [77]. However, in contrast to β-adrenergic inhibition, GCR antagonism did not prevent pneumonia. A very recent study now reported similar findings demonstrating in experimental stroke that the inhibition of glucocorticoid effects reversed lymphocytopenia while inhibition of β2AR restored interferon release in lymphocytes [78].

Do stress hormones mimic SIIA in vitro?

As reviewed in the preceding sections, clinical data and animal models suggest that catecholamines are the major mediator of SIIA. However, it is difficult to prove causality due to the complex pathways activated in whole animals and in patients. In vitro studies could provide complementary evidence if the effects observed in vivo could be replicated in vitro.

Table 3. Immune alterations immediately after disease onset.

	Ischemic stroke (IS)		Traumatic brain injury (TBI)		Myocardial infarction (MI)		(Surgical) trauma (ST/T)	
	animal	human	animal	human	animal	human	animal	human
innate immune system								
White blood cell		↑[98, 100]		↑[101]	↑[102]	↑[98, 103]		
monocytic HLA-DR		↓[98, 100, 104]				↓[98]	↓[105, 106]	↓[106, 107]
monocytic LPS activatability		↓[98, 104]				↓[98]		↓[108]
cytokines								
IL-10		↑[104, 109]	↑[110]	↑[94]		↑[43]		↑[111]
TNF-α	↓[77]	↓[100]	↑[110]			↓[98]	↑[112]	
IL-6		↑[98, 109]	↑[110]	↑[101, 113]	↑[98, 102]		↑[112]	↑[111]
HMGB-1		↑[76, 99]		↑[114]		↑[99]		↑[95, 115]
adaptive immune system								
circulatory lymphocyte number	↓[77]	↓[7, 100, 109, 116, 117]		↓[113]		↓[98]	↓[105, 106]	↓[107]
T lymphocyte activation		↓[116] ↑[76]				↑[118]		
IgG, IgM		=[117]		↓[119, 120]				
T-cell proliferation to mitogen		↓[117] =[76]		↓[113]				
hormones								
catecholamines	↑[77]	↑[4, 75, 76, 109]		↑[94]		↑[96, 97]		↑[95]
cortisol/corticosterone	↑[77]	↑[100, 104]				↑[98]	↑[106]	

LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

In peripheral blood mononuclear cells activated through the T-cell receptor in vitro, non-toxic concentrations of norepinephrine induce pro- and anti-inflammatory cytokine expression [93], while the synthetic glucocorticoid dexamethasone reduces cellular activation, lowering the number of cytokine-producing lymphocytes and inhibiting both Th1- and Th2-type cytokines [93]. In this setting, which included the combined in vitro application of dexamethasone and norepinephrine, the dexamethasone-induced alteration dominated [93]. Exposure to norepinephrine or terbutaline, a β2AR agonist, before T-cell receptor stimulation inhibits IFNγ production, as evident in the defective IFNγ response after stroke [12].

However, when peripheral blood mononuclear cells are not activated via the T-cell receptor but through the Toll-like receptors, application of dexamethasone and norepinephrine in vitro did not alter cytokine secretion (A. Kasprik, A. Dressel unpublished observations). These findings suggest that stress hormones may alter immune responses in a manner that is dependent on the activation pathway. We have observed that the in vitro application of catecholamines results in defunct upregulation of CTLA-4 expression on CD4+ T cells upon activation,

mimicking observations made in stroke patients [76]. Whether this impaired regulation of CTLA-4 is functionally relevant in stroke patients is not known.

Mechanisms of immunosuppression in various diseases

The preceding sections have summarized the currently available evidence on stress hormones and SIIA. Taken together, these data suggest that catecholamines and glucocorticoids are key factors inducing immunosuppression in cerebral ischemia, enhancing susceptibility to SIA. If this emerging pathophysiological concept is correct, the immunological alterations seen in SIIA may not be unique to ischemic stroke, but may extend to other diseases that also induce an acute release of catecholamines and glucocorticoids. A rapid increase in the plasma levels of catecholamines and steroids has long been described in TBI, MI, and surgical trauma and trauma (ST/T), among others [94-97]. Furthermore, a relationship between clinical outcome and initial catecholamine levels has been described for ST/T, similar to the relationship detected in stroke [4, 75, 76, 95]. To the best of our knowledge only two studies have compared

immune alterations in stroke and MI [98, 99]. We therefore reviewed publications addressing immunosuppressive mechanisms in TBI, MI, or ST/T. Cross-study comparisons have limited validity, as patient characteristics, time points of sample acquisition, assays used to determine the activation status, and measured cytokines differ between studies. Despite these limitations, there is a striking consistency in the pattern of immune alterations observed within 48 h after disease onset. These patterns are summarized in Table 3 and detailed in section 4.1 and 4.3.

Immune response and cytokines

ST/T, MI, and TBI induce increased white blood cell counts and reduced monocytic HLA-DR, similar to findings in cerebral ischemia [7, 94, 95, 98, 101, 103, 106]. Monocytic TNF-α production upon lipopolysaccharide challenge is diminished in ischemic stroke as well as in TBI. The proinflammatory cytokine IL-6 is upregulated in ischemic stroke, TBI, and MI, as is the antiinflammatory cytokine IL-10 [98, 101, 110, 111]. Furthermore HMGB1 which has been shown to be a strong proinflammatory mediator is also elevated in TBI, ST/T, and ischemic stroke [76, 95, 115, 121, 122].

The reduced number of circulatory T lymphocytes (CD4+, CD8+) is an overall phenomenon observed in ischemic stroke, TBI, MI, and ST/T. While proliferation in response to mitogenic stimuli is impaired in TBI [113] and surgery [123], it is indistinguishable from controls in ischemic stroke, where T cells are prone to proinflammation [76] or reported to be also impaired [117]. In TBI, even B cells are unable to mount normal IgM or IgG responses [119, 120].

Gut barrier

TBI was reported to lead to secondary infections in up to 75% of affected comatose patients [120]. One possible shared source of bacterial infections is endogenous bacteria, Escherichia coli translocated from the patient's own gut. Increased permeability was reported in experimental ischemic stroke, in TBI [124], in intracerebral hemorrhage [125], and in patients who underwent surgical trauma [126-128]. Vagal nerve stimulation was found to inhibit bacterial translocation in TBI [129].

Hormones

Increased catecholamine or cortisol/corticosterone levels are present very early after disease onset in all of the reviewed diseases (ischemic stroke, TBI, MI, ST/T) [4, 75, 76, 94-98, 100, 104, 106, 109]. The blockade of

catecholamine effects through the administration of propranolol was beneficial in ischemic stroke and in TBI [77, 94]. For TBI, beta blockade therapy is also suggested to be beneficial [130]. However, the effect of beta-blockade premedication in ischemic stroke patients is still not well enough investigated to draw conclusions. The levels of catecholamines 1 h post trauma (controls 0.3 ng/mL vs. TBI 3.27 ng/mL) correlate with mortality [95], while the results for TBI are contradictory [131, 132].

Summary and conclusion

Stress hormones are important regulators of immune cell function via adreneoreceptors and GCR. Lymphoid organs are directly innervated and nerve terminals release catecholamines. Moreover immune cells can actively secret hormones. There is strong evidence that the increase of stress hormones early after stroke is a marker for the extent of SIIA that can be expected to develop. Surprisingly, the experimental evidence suggests that catecholamine-triggered pathways, but not well-known immunosuppressive glucocorticoid-induced alterations, are causally related to SAI. However, which immune alterations induced by catecholamines mediate the enhanced susceptibility to infection in stroke patients remains to be determined. A recent observation from our laboratory provides evidence that catecholamine induced immune alterations are not limited to lymphocytes and monocytes but may extend to granulocyte function. The ability of monocytes and granulocytes to generate oxygen radicals (oxidative burst) was impaired in stroke patients compared to healthy controls. In vitro data suggest that catecholamines and glucocorticoids can both reduce oxidative burst [133].

In stroke and TBI, the brain injury itself is thought to trigger rapid activation of the stress pathways. MI patients suffer from thoracic pain and possibly respiratory distress, triggering a stress response in the absence of brain damage; similarly, patients with trauma also experience acute stress due to the trauma and to the resulting injury. Cross-study comparisons of ischemic stroke and TBI with ST/T and MI suggest that these diseases lead to similar induction of immunosuppression and subsequent infection through common activation of the stress response independently of direct central nervous system involvement (Figure 1).

Due to the similarities observed in alterations to the immune system in these very different diseases, we propose that SIIAs constitute a common response of the immune system to acute stress. SIIAs, which currently refer to "stroke-induced immune alterations", may therefore be better termed as "stress-induced immune alterations." Direct comparisons of the stress-induced immune alterations in various diseases are required to test

this hypothesis, which would offer a common therapeutic target to prevent infection and improve patient outcome across a wide spectrum of acute diseases.

Competing Interests

The authors declare that no competing interests exist.

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References

[1]   Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet, 367: 1747-1757

[2]   Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. (2010). Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation, 121: 948-954

[3]   Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 380: 2197-2223

[4]   Harms H, Reimnitz P, Bohner G, Werich T, Klingebiel R, Meisel C, et al. (2011). Influence of stroke localization on autonomic activation, immunodepression, and post-stroke infection. Cerebrovasc Dis, 32: 552-560

[5]   Vermeij FH, Scholte op Reimer WJ, de Man P, van Oostenbrugge RJ, Franke CL, de Jong G, et al. (2009). Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands Stroke Survey. Cerebrovasc Dis, 27: 465-471

[6]   Dirnagl U, Klehmet J, Braun JS, Harms H, Meisel C, Ziemssen T, et al. (2007). Stroke-induced immunodepression: experimental evidence and clinical relevance. Stroke, 38: 770-773

[7]   Vogelgesang A, Grunwald U, Langner S, Jack R, Broker BM, Kessler C, et al. (2008). Analysis of lymphocyte subsets in patients with stroke and their influence on infection after stroke. Stroke, 39: 237-241

[8]   Urra X, Obach V, Chamorro A (2009). Stroke induced immunodepression syndrome: from bench to bedside. Curr Mol Med, 9: 195-202

[9]   Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U (2005). Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci, 6: 775-786

[10]   Straub RH, Westermann J, Scholmerich J, Falk W (1998). Dialogue between the CNS and the immune system in lymphoid organs. Immunol Today, 19: 409-413

[11]   Kohm AP, Sanders VM (1999). Suppression of antigen-specific Th2 cell-dependent IgM and IgG1 production following norepinephrine depletion in vivo. J Immunol, 162: 5299-5308

[12]   Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE (1997). Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. J Immunol, 158: 4200-4210

[13]   Ramer-Quinn DS, Baker RA, Sanders VM (1997). Activated T helper 1 and T helper 2 cells differentially express the beta-2-adrenergic receptor: a mechanism for selective modulation of T helper 1 cell cytokine production. J Immunol, 159: 4857-4867

[14]   Charlene A. McQueen, editor. Comprehensive Toxicology, Kidlington: Elsevier Science & Technology; 2010

[15]   Dunn AJ (1995). Interactions Between the Nervous System and the Immune System: Implications for Psychopharmacology. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: The Fourth Generation of Progress, Lippincott Williams and Wilkins.

[16]   Musso NR, Brenci S, Setti M, Indiveri F, Lotti G (1996). Catecholamine content and in vitro catecholamine synthesis in peripheral human lymphocytes. J Clin Endocrinol Metab, 81: 3553-3557

[17]   Josefsson E, Bergquist J, Ekman R, Tarkowski A (1996). Catecholamines are synthesized by mouse lymphocytes and regulate function of these cells by induction of apoptosis. Immunology, 88: 140-146

[18]   Bergquist J, Tarkowski A, Ekman R, Ewing A (1994). Discovery of endogenous catecholamines in lymphocytes and evidence for catecholamine regulation of lymphocyte function via an autocrine loop. Proc Natl Acad Sci U S A, 91: 12912-12916

[19]   Flierl MA, Rittirsch D, Huber-Lang M, Sarma JV, Ward PA (2008). Catecholamines-crafty weapons in the inflammatory arsenal of immune/inflammatory cells or opening pandora's box? Mol Med, 14: 195-204

[20]   Benschop RJ, Rodriguez-Feuerhahn M, Schedlowski M (1996). Catecholamine-induced leukocytosis: early observations, current research, and future directions. Brain, behavior, and immunity, 10: 77-91

[21] Sanders VM (2012). The beta2-adrenergic receptor on T and B lymphocytes: do we understand it yet? Brain, behavior, and immunity, 26: 195-200

[22] Kin NW, Sanders VM (2006). It takes nerve to tell T and B cells what to do. Journal of leukocyte biology, 79: 1093-1104

[23] Straub RH (2004). Complexity of the bi-directional neuroimmune junction in the spleen. Trends Pharmacol Sci, 25: 640-646

[24] Pratt WB, Toft DO (2003). Regulation of signaling protein function and trafficking by the hsp90/hsp70-based chaperone machinery. Exp Biol Med (Maywood), 228: 111-133

[25] Zhou J, Cidlowski JA (2005). The human glucocorticoid receptor: one gene, multiple proteins and diverse responses. Steroids, 70: 407-417

[26] Lowenberg M, Stahn C, Hommes DW, Buttgereit F (2008). Novel insights into mechanisms of glucocorticoid action and the development of new glucocorticoid receptor ligands. Steroids, 73: 1025-1029

[27] De Bosscher K, Haegeman G (2009). Minireview: latest perspectives on antiinflammatory actions of glucocorticoids. Mol Endocrinol, 23: 281-291

[28] Baschant U, Tuckermann J (2010). The role of the glucocorticoid receptor in inflammation and immunity. J Steroid Biochem Mol Biol, 120: 69-75

[29] Moser M, De Smedt T, Sornasse T, Tielemans F, Chentoufi AA, Muraille E, et al. (1995). Glucocorticoids down-regulate dendritic cell function in vitro and in vivo. European journal of immunology, 25: 2818-2824

[30] Kitajima T, Ariizumi K, Bergstresser PR, Takashima A (1996). A novel mechanism of glucocorticoid-induced immune suppression: the inhibiton of T cell-mediated terminal maturation of a murine dendritic cell line. The Journal of clinical investigation, 98: 142-147

[31] Matyszak MK, Citterio S, Rescigno M, Ricciardi-Castagnoli P (2000). Differential effects of corticosteroids during different stages of dendritic cell maturation. European journal of immunology, 30: 1233-1242

[32] Tuckermann JP, Kleiman A, Moriggl R, Spanbroek R, Neumann A, Illing A, et al. (2007). Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. The Journal of clinical investigation, 117: 1381-1390

[33] Cumberbatch M, Dearman RJ, Kimber I (1999). Inhibition by dexamethasone of Langerhans cell migration: influence of epidermal cytokine signals. Immunopharmacology, 41: 235-243

[34] Vizzardelli C, Pavelka N, Luchini A, Zanoni I, Bendickson L, Pelizzola M, et al. (2006). Effects of dexamethazone on LPS-induced activationand migration of mouse dendritic cells revealed by a genome-wide transcriptional analysis. European journal of immunology, 36: 1504-1515

[35] Rutella S, Danese S, Leone G (2006). Tolerogenic dendritic cells: cytokine modulation comes of age. Blood, 108: 1435-1440

[36] Kim BJ, Jones HP (2010). Epinephrine-primed murine bone marrow-derived dendritic cells facilitate production of IL-17A and IL-4 but not IFN-gamma by CD4+ T cells. Brain, behavior, and immunity, 24: 1126-1136

[37] Maestroni GJ (2000). Dendritic cell migration controlled by alpha 1b-adrenergic receptors. J Immunol, 165: 6743-6747

[38] Maestroni GJ (2002). Short exposure of maturing, bone marrow-derived dendritic cells to norepinephrine: impact on kinetics of cytokine production and Th development. Journal of neuroimmunology, 129: 106-114

[39] Yanagawa Y, Matsumoto M, Togashi H (2011). Adrenoceptor-mediated enhancement of interleukin-33 production by dendritic cells. Brain, behavior, and immunity, 25: 1427-1433

[40] Goyarts E, Matsui M, Mammone T, Bender AM, Wagner JA, Maes D, et al. (2008). Norepinephrine modulates human dendritic cell activation by altering cytokine release. Experimental dermatology, 17: 188-196

[41] Ehrchen J, Steinmuller L, Barczyk K, Tenbrock K, Nacken W, Eisenacher M, et al. (2007). Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. Blood, 109: 1265-1274

[42] Varga G, Ehrchen J, Tsianakas A, Tenbrock K, Rattenholl A, Seeliger S, et al. (2008). Glucocorticoids induce an activated, anti-inflammatory monocyte subset in mice that resembles myeloid-derived suppressor cells. Journal of leukocyte biology, 84: 644-650

[43] Platzer C, Docke W, Volk H, Prosch S (2000). Catecholamines trigger IL-10 release in acute systemic stress reaction by direct stimulation of its promoter/enhancer activity in monocytic cells. Journal of neuroimmunology, 105: 31-38

[44] Rainer TH, Lam N, Cocks RA (1999). Adrenaline upregulates monocyte L-selectin in vitro. Resuscitation, 43: 47-55

[45] Straub RH, Herrmann M, Berkmiller G, Frauenholz T, Lang B, Scholmerich J, et al. (1997). Neuronal regulation of interleukin 6 secretion in murine spleen: adrenergic and opioidergic control. Journal of neurochemistry, 68: 1633-1639

[46] Straub RH, Dorner M, Riedel J, Kubitza M, Van Rooijen N, Lang B, et al. (1998). Tonic neurogenic inhibition of interleukin-6 secretion from murine spleen caused by

opioidergic transmission. The American journal of physiology, 274: R997-1003

[47]　Pitzalis C, Pipitone N, Perretti M (2002). Regulation of leukocyte-endothelial interactions by glucocorticoids. Annals of the New York Academy of Sciences, 966: 108-118

[48]　Stroncek DF, Yau YY, Oblitas J, Leitman SF (2001). Administration of G--CSF plus dexamethasone produces greater granulocyte concentrate yields while causing no more donor toxicity than G--CSF alone. Transfusion, 41: 1037-1044

[49]　Heasman SJ, Giles KM, Ward C, Rossi AG, Haslett C, Dransfield I (2003). Glucocorticoid-mediated regulation of granulocyte apoptosis and macrophage phagocytosis of apoptotic cells: implications for the resolution of inflammation. The Journal of endocrinology, 178: 29-36

[50]　Parks KR, Davis JM (2012). Epinephrine, cortisol, endotoxin, nutrition, and the neutrophil. Surgical infections, 13: 300-306

[51]　Giraldo E, Multhoff G, Ortega E (2010). Noradrenaline increases the expression and release of Hsp72 by human neutrophils. Brain, behavior, and immunity, 24: 672-677

[52]　Trabold B, Gruber M, Frohlich D (2007). Functional and phenotypic changes in polymorphonuclear neutrophils induced by catecholamines. Scandinavian cardiovascular journal : SCJ, 41: 59-64

[53]　Kaufmann I, Eisner C, Richter P, Huge V, Beyer A, Chouker A, et al. (2007). Psychoneuroendocrine stress response may impair neutrophil function in complex regional pain syndrome. Clin Immunol, 125: 103-111

[54]　Cupps TR, Edgar LC, Thomas CA, Fauci AS (1984). Multiple mechanisms of B cell immunoregulation in man after administration of in vivo corticosteroids. J Immunol, 132: 170-175

[55]　Cupps TR, Gerrard TL, Falkoff RJ, Whalen G, Fauci AS (1985). Effects of in vitro corticosteroids on B cell activation, proliferation, and differentiation. The Journal of clinical investigation, 75: 754-761

[56]　Kasprowicz DJ, Kohm AP, Berton MT, Chruscinski AJ, Sharpe A, Sanders VM (2000). Stimulation of the B cell receptor, CD86 (B7-2), and the beta 2-adrenergic receptor intrinsically modulates the level of IgG1 and IgE produced per B cell. J Immunol, 165: 680-690

[57]　Kohm AP, Mozaffarian A, Sanders VM (2002). B cell receptor- and beta 2-adrenergic receptor-induced regulation of B7-2 (CD86) expression in B cells. J Immunol, 168: 6314-6322

[58]　Pongratz G, McAlees JW, Conrad DH, Erbe RS, Haas KM, Sanders VM (2006). The level of IgE produced by a B cell is regulated by norepinephrine in a p38 MAPK- and CD23-dependent manner. J Immunol, 177: 2926-2938

[59]　Wang D, Muller N, McPherson KG, Reichardt HM (2006). Glucocorticoids engage different signal transduction pathways to induce apoptosis in thymocytes and mature T cells. J Immunol, 176: 1695-1702

[60]　Chen X, Murakami T, Oppenheim JJ, Howard OM (2004). Differential response of murine CD4+CD25+ and CD4+CD25- T cells to dexamethasone-induced cell death. European journal of immunology, 34: 859-869

[61]　Ramirez F, Fowell DJ, Puklavec M, Simmonds S, Mason D (1996). Glucocorticoids promote a TH2 cytokine response by CD4+ T cells in vitro. J Immunol, 156: 2406-2412

[62]　Momcilovic M, Miljkovic Z, Popadic D, Markovic M, Savic E, Ramic Z, et al. (2008). Methylprednisolone inhibits interleukin-17 and interferon-gamma expression by both naive and primed T cells. BMC immunology, 9: 47

[63]　Franchimont D, Galon J, Gadina M, Visconti R, Zhou Y, Aringer M, et al. (2000). Inhibition of Th1 immune response by glucocorticoids: dexamethasone selectively inhibits IL-12-induced Stat4 phosphorylation in T lymphocytes. J Immunol, 164: 1768-1774

[64]　Liberman AC, Druker J, Refojo D, Holsboer F, Arzt E (2009). Glucocorticoids inhibit GATA-3 phosphorylation and activity in T cells. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 23: 1558-1571

[65]　Maneechotesuwan K, Yao X, Ito K, Jazrawi E, Usmani OS, Adcock IM, et al. (2009). Suppression of GATA-3 nuclear import and phosphorylation: a novel mechanism of corticosteroid action in allergic disease. PLoS medicine, 6: e1000076

[66]　Biola A, Andreau K, David M, Sturm M, Haake M, Bertoglio J, et al. (2000). The glucocorticoid receptor and STAT6 physically and functionally interact in T-lymphocytes. FEBS letters, 487: 229-233

[67]　Swanson MA, Lee WT, Sanders VM (2001). IFN-gamma production by Th1 cells generated from naive CD4+ T cells exposed to norepinephrine. J Immunol, 166: 232-240

[68]　Bush KA, Krukowski K, Eddy JL, Janusek LW, Mathews HL (2012). Glucocorticoid receptor mediated suppression of natural killer cell activity: identification of associated deacetylase and corepressor molecules. Cellular immunology, 275: 80-89

[69]　Gan X, Zhang L, Solomon GF, Bonavida B (2002). Mechanism of norepinephrine-mediated inhibition of human NK cytotoxic functions: inhibition of cytokine secretion, target binding, and programming for cytotoxicity. Brain, behavior, and immunity, 16: 227-246

[70]　Brait VH, Arumugam TV, Drummond GR, Sobey CG (2012). Importance of T lymphocytes in brain injury, immunodeficiency, and recovery after cerebral ischemia. J Cereb Blood Flow Metab, 32: 598-611

[71] Morganti-Kossmann MC, Satgunaseelan L, Bye N, Kossmann T (2007). Modulation of immune response by head injury. Injury, 38: 1392-1400

[72] Morganti-Kossmann MC, Rancan M, Stahel PF, Kossmann T (2002). Inflammatory response in acute traumatic brain injury: a double-edged sword. Curr Opin Crit Care, 8: 101-105

[73] Kamel H, Iadecola C (2012). Brain-immune interactions and ischemic stroke: clinical implications. Arch Neurol, 69: 576-581

[74] Whiting MJ, Doogue MP (2009). Advances in biochemical screening for phaeochromocytoma using biogenic amines. Clin Biochem Rev, 30: 3-17

[75] Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Gomez-Choco M, et al. (2007). Catecholamines, infection, and death in acute ischemic stroke. J Neurol Sci, 252: 29-35

[76] Vogelgesang A, May VE, Grunwald U, Bakkeboe M, Langner S, Wallaschofski H, et al. (2010). Functional status of peripheral blood T-cells in ischemic stroke patients. PLoS One, 5: e8718

[77] Prass K, Meisel C, Hoflich C, Braun J, Halle E, Wolf T, et al. (2003). Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med, 198: 725-736

[78] Mracsko E, Liesz A, Karcher S, Zorn M, Bari F, Veltkamp R (2014). Differential effects of sympathetic nervous system and hypothalamic-pituitary-adrenal axis on systemic immune cells after severe experimental stroke. Brain, behavior, and immunity,

[79] Wong CH, Jenne CN, Lee WY, Leger C, Kubes P (2011). Functional innervation of hepatic iNKT cells is immunosuppressive following stroke. Science, 334: 101-105

[80] Ajmo CT, Jr., Collier LA, Leonardo CC, Hall AA, Green SM, Womble TA, et al. (2009). Blockade of adrenoreceptors inhibits the splenic response to stroke. Exp Neurol, 218: 47-55

[81] Fassbender K, Schmidt R, Mossner R, Daffertshofer M, Hennerici M (1994). Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke, 25: 1105-1108

[82] Franceschini R, Gandolfo C, Cataldi A, Del Sette M, Cianciosi P, Finocchi C, et al. (1994). Twenty-four-hour beta-endorphin secretory pattern in stroke patients. Stroke, 25: 2142-2145

[83] Olsson T (1990). Urinary free cortisol excretion shortly after ischaemic stroke. J Intern Med, 228: 177-181

[84] Emsley H (2003). An early and sustained peripheral inflammatory response in acute ischaemic stroke: relationships with infection and atherosclerosis. Journal of neuroimmunology, 139: 93-101

[85] Marklund N, Peltonen M, Nilsson TK, Olsson T (2004). Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J Intern Med, 256: 15-21

[86] Neidert S, Katan M, Schuetz P, Fluri F, Ernst A, Bingisser R, et al. (2011). Anterior pituitary axis hormones and outcome in acute ischaemic stroke. J Intern Med, 269: 420-432

[87] Christensen H, Boysen G, Johannesen HH (2004). Serum-cortisol reflects severity and mortality in acute stroke. J Neurol Sci, 217: 175-180

[88] O'Neill PA, Davies I, Fullerton KJ, Bennett D (1991). Stress hormone and blood glucose response following acute stroke in the elderly. Stroke, 22: 842-847

[89] Murros K, Fogelholm R, Kettunen S, Vuorela AL (1993). Serum cortisol and outcome of ischemic brain infarction. J Neurol Sci, 116: 12-17

[90] Anne M, Juha K, Timo M, Mikko T, Olli V, Kyosti S, et al. (2007). Neurohormonal activation in ischemic stroke: effects of acute phase disturbances on long-term mortality. Curr Neurovasc Res, 4: 170-175

[91] Szczudlik A, Dziedzic T, Bartus S, Slowik A, Kieltyka A (2004). Serum interleukin-6 predicts cortisol release in acute stroke patients. J Endocrinol Invest, 27: 37-41

[92] Weidenfeld J, Leker RR, Gai N, Teichner A, Bener D, Ovadia H (2011). The function of the adrenocortical axis in permanent middle cerebral artery occlusion: effect of glucocorticoids on the neurological outcome. Brain Res, 1407: 90-96

[93] Torres KC, Antonelli LR, Souza AL, Teixeira MM, Dutra WO, Gollob KJ (2005). Norepinephrine, dopamine and dexamethasone modulate discrete leukocyte subpopulations and cytokine profiles from human PBMC. Journal of neuroimmunology, 166: 144-157

[94] Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, et al. (1998). Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. Nat Med, 4: 808-813

[95] Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR (2012). High circulating adrenaline levels at admission predict increased mortality after trauma. The journal of trauma and acute care surgery, 72: 428-436

[96] Ostrowski SR, Pedersen SH, Jensen JS, Mogelvang R, Johansson PI (2013). Acute myocardial infarction is associated with endothelial glycocalyx and cell damage and a parallel increase in circulating catecholamines. Crit Care, 17: R32

[97] Christensen NJ, Videbaek J (1974). Plasma catecholamines and carbohydrate metabolism in patients

with acute myocardial infarction. The Journal of clinical investigation, 54: 278-286

[98] Haeusler KG, Schmidt WU, Foehring F, Meisel C, Guenther C, Brunecker P, et al. (2012). Immune responses after acute ischemic stroke or myocardial infarction. Int J Cardiol, 155: 372-377

[99] Goldstein RS, Gallowitsch-Puerta M, Yang L, Rosas-Ballina M, Huston JM, Czura CJ, et al. (2006). Elevated high-mobility group box 1 levels in patients with cerebral and myocardial ischemia. Shock, 25: 571-574

[100] Haeusler KG, Schmidt WU, Fohring F, Meisel C, Helms T, Jungehulsing GJ, et al. (2008). Cellular immunodepression preceding infectious complications after acute ischemic stroke in humans. Cerebrovasc Dis, 25: 50-58

[101] Kossmann T, Hans VH, Imhof HG, Stocker R, Grob P, Trentz O, et al. (1995). Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. Shock, 4: 311-317

[102] Ruparelia N, Digby JE, Jefferson A, Medway DJ, Neubauer S, Lygate CA, et al. (2013). Myocardial infarction causes inflammation and leukocyte recruitment at remote sites in the myocardium and in the renal glomerulus. Inflammation research: official journal of the European Histamine Research Society ... [et al.], 62: 515-525

[103] Fukui D, Yasukawa H, Sugi Y, Oba T, Nagata T, Kyogoku S, et al. (2012). Transient reduction and activation of circulating dendritic cells in patients with acute myocardial infarction. Int J Cardiol, 160: 216-219

[104] Urra X, Cervera A, Obach V, Climent N, Planas AM, Chamorro A (2009). Monocytes are major players in the prognosis and risk of infection after acute stroke. Stroke, 40: 1262-1268

[105] Riegger T, Conrad S, Liu K, Schluesener HJ, Adibzahdeh M, Schwab JM (2007). Spinal cord injury-induced immune depression syndrome (SCI-IDS). The European journal of neuroscience, 25: 1743-1747

[106] Menges P, Kessler W, Kloecker C, Feuerherd M, Gaubert S, Diedrich S, et al. (2012). Surgical trauma and postoperative immune dysfunction. Eur Surg Res, 48: 180-186

[107] Riegger T, Conrad S, Schluesener HJ, Kaps HP, Badke A, Baron C, et al. (2009). Immune depression syndrome following human spinal cord injury (SCI): a pilot study. Neuroscience, 158: 1194-1199

[108] Kirchhoff C, Biberthaler P, Mutschler WE, Faist E, Jochum M, Zedler S (2009). Early down-regulation of the pro-inflammatory potential of monocytes is correlated to organ dysfunction in patients after severe multiple injury: a cohort study. Crit Care, 13: R88

[109] Klehmet J, Harms H, Richter M, Prass K, Volk HD, Dirnagl U, et al. (2009). Stroke-induced immunodepression and post-stroke infections: lessons

from the preventive antibacterial therapy in stroke trial. Neuroscience, 158: 1184-1193

[110] Li M, Li F, Luo C, Shan Y, Zhang L, Qian Z, et al. (2011). Immediate splenectomy decreases mortality and improves cognitive function of rats after severe traumatic brain injury. J Trauma, 71: 141-147

[111] Silveira FP, Nicoluzzi JE, Saucedo Junior NS, Silveira F, Nicollelli GM, Maranhao BS (2012). Evaluation of serum levels of interleukin-6 and interleukin-10 in patients undergoing laparoscopic versus conventional cholecystectomy. Rev Col Bras Cir, 39: 33-40

[112] Chu W, Li M, Li F, Hu R, Chen Z, Lin J, et al. (2013). Immediate splenectomy down-regulates the MAPK-NF-kappaB signaling pathway in rat brain after severe traumatic brain injury. The journal of trauma and acute care surgery, 74: 1446-1453

[113] Dziedzic T, Slowik A, Szczudlik A (2004). Nosocomial infections and immunity: lesson from brain-injured patients. Crit Care, 8: 266-270

[114] Wang KY, Yu GF, Zhang ZY, Huang Q, Dong XQ (2012). Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. Clinica chimica acta; international journal of clinical chemistry, 413: 1737-1741

[115] Peltz ED, Moore EE, Eckels PC, Damle SS, Tsuruta Y, Johnson JL, et al. (2009). HMGB1 is markedly elevated within 6 hours of mechanical trauma in humans. Shock, 32: 17-22

[116] Urra X, Cervera A, Villamor N, Planas AM, Chamorro A (2009). Harms and benefits of lymphocyte subpopulations in patients with acute stroke. Neuroscience, 158: 1174-1183

[117] Czlonkowska A, Korlak J (1979). [Humoral immune response in patients with stroke]. Pol Tyg Lek, 34: 485-487

[118] Cheng X, Liao YH, Ge H, Li B, Zhang J, Yuan J, et al. (2005). TH1/TH2 functional imbalance after acute myocardial infarction: coronary arterial inflammation or myocardial inflammation. Journal of clinical immunology, 25: 246-253

[119] Griffin GD (2011). The injured brain: TBI, mTBI, the immune system, and infection: connecting the dots. Mil Med, 176: 364-368

[120] Wolach B, Sazbon L, Gavrieli R, Broda A, Schlesinger M (2001). Early immunological defects in comatose patients after acute brain injury. J Neurosurg, 94: 706-711

[121] Schulze J, Zierath D, Tanzi P, Cain K, Shibata D, Dressel A, et al. (2013). Severe stroke induces long-lasting alterations of high-mobility group box 1. Stroke, 44: 246-248

[122] Kawabata H, Setoguchi T, Yone K, Souda M, Yoshida H, Kawahara K, et al. (2010). High mobility group box 1 is upregulated after spinal cord injury and is associated

with neuronal cell apoptosis. Spine (Phila Pa 1976), 35: 1109-1115

[123] Angele MK, Chaudry IH (2005). Surgical trauma and immunosuppression: pathophysiology and potential immunomodulatory approaches. Langenbecks Arch Surg, 390: 333-341

[124] Castillo L, Velasco N, Wainstein C, Bugedo G, Hernandez G, Klaassen J, et al. (1999). [Transcranial cytokine gradient and intestinal permeability in acute severe brain injury]. Rev Med Chil, 127: 639-646

[125] Hernandez G, Hasbun P, Velasco N, Wainstein C, Bugedo G, Bruhn A, et al. (2007). Splanchnic ischemia and gut permeability after acute brain injury secondary to intracranial hemorrhage. Neurocrit Care, 7: 40-44

[126] Jiang XH, Li N, Li JS (2003). Intestinal permeability in patients after surgical trauma and effect of enteral nutrition versus parenteral nutrition. World J Gastroenterol, 9: 1878-1880

[127] O'Boyle CJ, MacFie J, Mitchell CJ, Johnstone D, Sagar PM, Sedman PC (1998). Microbiology of bacterial translocation in humans. Gut, 42: 29-35

[128] MacFie J (1997). Bacterial translocation in surgical patients. Ann R Coll Surg Engl, 79: 183-189

[129] Bansal V, Costantini T, Ryu SY, Peterson C, Loomis W, Putnam J, et al. (2010). Stimulating the central nervous system to prevent intestinal dysfunction after traumatic brain injury. J Trauma, 68: 1059-1064

[130] Heffernan DS, Inaba K, Arbabi S, Cotton BA (2010). Sympathetic hyperactivity after traumatic brain injury and the role of beta-blocker therapy. J Trauma, 69: 1602-1609

[131] Salehpoor F, Bazzazi AM, Estakhri R, Zaheri M, Asghari B (2010). Correlation between catecholamine levels and outcome in patients with severe head trauma. Pak J Biol Sci, 13: 738-742

[132] Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV (1987). The predictive value of catecholamines in assessing outcome in traumatic brain injury. J Neurosurg, 66: 875-882

[133] Ruhnau J, Schulze K, Gaida B, Langner S, Kessler C, Broker B, et al. (2014). Stroke alters respiratory burst in neutrophils and monocytes. Stroke, 45: 794-800